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EXAMINER
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SAOUD, CHRISTINE J

ART UNIT	PAPER NUMBER
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1647

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Please find below and/or attached an Office communication concerning this application or proceeding.



## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 14 February 2006 has been entered.

Claims 3, 5-7, 11-14, 16, 17, and 21-22 are pending and under examination. Claims 21-22 have been amended as requested in the paper filed 14 February 2006.

### ***Drawings***

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

The instant specification does not include the proper section headings; at least "BRIEF DESCRIPTION OF THE DRAWINGS" is missing. Applicant is required to review the entire specification to be sure it meets the requirements of 37 CFR 1.77(b).

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

### **Arrangement of the Specification**

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

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- (a) TITLE OF THE INVENTION.
- (b) CROSS-REFERENCE TO RELATED APPLICATIONS.
- (c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
- (d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT
- (e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
- (f) BACKGROUND OF THE INVENTION.
  - (1) Field of the Invention.
  - (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (g) BRIEF SUMMARY OF THE INVENTION.
- (h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
- (i) DETAILED DESCRIPTION OF THE INVENTION.
- (j) CLAIM OR CLAIMS (commencing on a separate sheet).
- (k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
- (l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-22 (and dependent claims 3, 5-7, 11-14, 16, 17) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

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inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 21-22 have been amended to include the proviso that “the production does not include a peptide refolding step after the addition of the metal salt”. The instant specification fails to provide support for this inventive concept. Additionally, there is no antecedent basis for “refolding step” in the instant specification as originally filed. Applicant points to page 2, lines 25-27 as basis for this limitation, however, this passage does not recite a refolding step. It is directed to the observation that trisulfides can be reduced by the addition of a metal salt, during or after fermentation and not “by conversion of the formed trisulfide of growth hormone into the native form”. There is no mention of “refolding step” and this passage does not exclude the presence of a refolding step, or any other step for that matter. This interpretation is supported by the passage in the specification at page 3, lines 1-2 which states that “addition can be done directly after fermentation, e.g. after the fermentation has been terminated and the cells are harvested and before further process steps”. The specification clearly indicates that further process steps were to be considered part of the invention and there is no proviso in the instant specification that would exclude a refolding step, therefore the new limitations directed to the proviso are considered new matter.

Claims 3, 5-7, 11-14, 16, 17, and 21-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require the measurement of the "pH of the cells". However, the pH of the cells would be roughly 7.0 and not less than 7.0. The specification has no basis for the "pH of the cells" in the instant claims. The pH that was measured in the specification was for the "cell concentrate". It would be reasonable for the pH of the concentrate to be different from 7.0, but not for the cells themselves. Furthermore, the specification is only limited to the "cell concentrate" being different from 7.0 and therefore, the claims should be amended to be directed to the pH of the cell concentrate.

### ***Claim Interpretation***

The claims are directed to a "method for production of recombinant growth hormone" or "peptides". The methods includes the steps of

- 1) fermenting cells to produce the growth hormone or peptides,
- 2) adding a metal salt during or after the fermenting step prior to isolation of the growth hormone or peptide,
- 3) wherein the pH of the cell concentrate after the addition of the metal salt is less than or equal to 7 (i.e. adjusting the pH after salt addition to a pH of 7 or less).

These method steps are to have the effect of "reducing the amount of trisulfides formed in the production of the recombinant peptide". This reduction in the amount of trisulfides is the result of the addition of the metal salt, as indicated by Applicant in the

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specification and in the arguments of record. Therefore, if a metal salt is added, it is expected to reduce the amount of trisulfides, regardless of whether the art is aware of this effect, absent evidence to the contrary.

Additionally, the method is written in "comprising" language, which allows for additional steps being present in the method. It is pointed out above that the "proviso" of the claims is new matter. It should also be pointed out that the language of the proviso does not exclude a protein refolding step if it is in conjunction with the addition of the metal salt (the limitation specifically states "after"). The art will be applied accordingly.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-7, 11-12, 14, 16-17, and 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Aviv et al. (U.S. Pat. No. 5,256,546).

Aviv et al. teach the production of recombinant human growth hormone. The production is performed in a medium containing  $K_2PO_4$  and NaCl as well as several other metal salts (see column 16, Example 4). These metal salts are added during fermentation because they are contained in the culture medium. The pH of the culture is maintained at 7 +/- 0.2, meeting the limitation that the pH be equal to or lower than

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7.0. Therefore, the limitations of the claims have been anticipated by the prior art of Aviv et al.

Claims 3, 5, 6, 11, 13, 14, 16, 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Yokoo et al. (U.S. Pat. No. 4,985,544).

Yokoo et al. teach a method for the production of growth hormone (from fish). The first portion of the method, prior to denaturing and renaturing, includes addition of an alkali metal or alkaline earth metal to a precipitate of growth hormone, which has been buffered to a pH of 7.0, and then isolation of the growth hormone in the form of purified inclusion bodies. See column 3, lines 15-35, lines 43-45, lines 63-65 and column 4, lines 15-17. This disclosure anticipates the instant claims.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 3, 6, 11-14, 16, 21-22 rejected under 35 U.S.C. 103(a) as being unpatentable over Christensen (WO 96/02570A1).

Christensen teaches a method for the production of recombinant human growth hormone (page 2, lines 14-19) which includes the addition of a sulfite (alkali metal sulphite, page 4, lines 17-21) for conversion of a hydrophobic derivative of a growth hormone into the native form of the growth hormone. The method is performed in a

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solvent which is buffered to a pH of about 7.0 (page 5, lines 10-17). Christensen teaches that the growth hormone may "optionally" be isolated before carrying out the conversion thereof into the corresponding native growth hormone (page 5, lines 4-6). Christensen also teaches that the growth hormone could be recombinantly produced by a microorganism such as *E. coli* (page 2)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the instant invention to have practiced the method of Christensen by producing growth hormone in a bacterium which includes fermentation, treating the growth hormone produced thereby with sodium sulphite at a pH of about 7, and then isolating the resulting native growth hormone. One would have been motivated to practice this method because for the administration of growth hormone therapeutically, it is desirable to have growth hormone which is in its native state, rather than derivatives which can cause undesirable side effects (see page 3, lines 13-16 of Christensen). One would also be motivated to practice the method of Christensen by choosing to add the sodium sulphite prior to growth hormone isolation because Christensen teach that this is one of two ways in which the method could be practiced. One would have a reasonable expectation of success in practicing the method with the desired result of obtaining the native form of growth hormone because Christensen teaches that addition of a sulfite to a sample of growth hormone reduces the presence of the trisulphide bridge (see page 17-18, Example).

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Claims 5-7, 11-14, 16-17 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al. (U.S. Pat. No. 5,663,304) for the reasons of record in the previous Office action.

Applicant argues at page 5 of the response that the goals of the method of Builder et al. are different from those of the instant invention because Builder et al. does not teach or suggest a method relating to the amount of trisulfides formed in the production of growth hormone or recombinant peptide. This argument has been considered, but is not persuasive. The claims are directed to a method – if the steps of the method are the same, then the end result should also be the same. Builder et al. relates his invention to correctly folded growth hormone. However, recombinant production of proteins in *E. coli* involves trisulfide bonding as evidenced by Applicant's own specification and Christensen (cited above). Therefore, the presence of a trisulfide bond in a recombinantly produced protein, such as growth hormone, would be inherent to the recombinant production of the protein. Applicant's method involves addition of an alkali metal salt at a pH of 7.0 or lower, which results in a reduction of trisulfides. However, the method of Builder et al. also involves the addition of an alkali metal salt at a pH of about 7. Builder et al. is silent to trisulfides, but the result of the addition of the alkali metal salt at pH 7 would be expected to be the same (i.e. inherent result of the addition). Applicant also argues that Builder et al. do not teach a method wherein the production does not include a refolding step. However, Builder et al. teach treatment of the protein and isolation of the protein BEFORE any protein refolding step is performed. Therefore, the fact that Builder et al. teaches additional method steps, these steps are

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performed after the “production” of the protein. As pointed out previously, the instant specification does not exclude additional process steps, and the additional step(s) of Builder et al. would be considered refolding, and not part of the “production”.

Applicant’s arguments at page 6 of the response have been considered, but are not persuasive. As pointed out above, Builder et al. teach the addition of an alkali metal salt at a pH of 7.0, and therefore, the critical limitations of the claims are met. Builder et al. teach additional method steps, but these additional steps can be separate from the “production” steps. They are undertaken after the protein is produced. Applicant’s reliance on solving a problem of trisulfide formation is misplaced – if the addition of an alkali metal salt at a pH of 7.0 reduces trisulfide formation, then the method of Builder et al. already solves this problem. Builder et al. does not need to teach that this is a problem. A patent cannot be granted purely because Applicant has discovered a new property of a compound or method. The method of Builder et al. produced a recombinant protein – it would inherently have reduced trisulfides compared to recombinant protein produced by another method which did not include addition of an alkali metal salt at a pH of 7.0 – therefore, the limitations of the claims are met.

Applicant argues at page 7 of the response that protein production in the method of Builder et al. only occurred after the depletion of phosphate. However, potassium phosphate is not the only alkali metal salt in the medium – potassium chloride is also present (see column 26, lines 60-66), therefore, this argument is not persuasive.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**CHRISTINE J. SAOUD  
PRIMARY EXAMINER**

*Christine J. Saoud*